REMARKS

Informality Objections

The Examiner objected to the specification because of missing cross-reference data. The relevant paragraphs in the specification have been amended to provide the cross-reference data.

The Examiner objected to the claims because of informalities arising from improper reference to antecedents. Applicant notes with appreciation the detailed suggestions that the Examiner made in the Office Action for correcting the informalities. The present claim amendments incorporate the Examiner's suggestions, and additional amendments to correct additional informalities noted by the Applicant.

Prior Art Rejections

The Examiner rejected claims 1-7 and 9-13 as being anticipated by U.S. Patent No. 5,324,401 to Yeung under 35 U.S.C. 102(b). In addition, the Examiner rejected claims 1-3 and 6-13 under 35 U.S.C. 102(b) as being anticipated by WO 01/02846 to Melman. These rejections are respectfully traversed.

a. Summary of the Invention

The present invention provides a multi-channel detection scheme for a bio-separation device, based on a multi-radiation source/common detector configuration, in which detection is conducted in a **time-staggered, and/or time-multiplexed detection** across the channels. A single detector is coupled to a plurality of radiation sources, in a one detector - many radiation

sources configuration. Each radiation source directs radiation at one detection zone of a single separation channel, and a single detector is applied to detect light emissions from the detection zones of several separation channels in a time-staggered manner. There may be more than one detector in the entire detection system, each serving multiple radiation sources.

Bio-separation may be conducted simultaneously in all the channels in parallel, with detection **time-staggered and/or time-multiplexed** with respect to the light sources. The light sources direct radiation at the detection zones in a predetermined sequence in a cyclic manner, with the detector output synchronized to the light sources by a controller. The radiation sources **and** the detector are pulsed in synchronization in a time-multiplexed manner. The controller controls the detector **and** radiation sources in a manner to effect detection of radiation emissions from the multiple separation channels in predetermined detection cycles, wherein **each detection cycle is repeated at a frequency to provide a desired detection time or duration**. The controller controls the radiation sources and detector in a manner to effect detection in a repeated scanning manner, across the detection zones of the separation channels, in a time-staggered type detection. In accordance with the present invention, cross talk between channels is virtually eliminated, thus improving signal to noise ratio.

b. 102(b) Rejection Based on Yeung

Applicant respectfully submits that Yeung does not teach all the features of the claimed invention, and therefore does not anticipate the invention as claimed.

Yeung is not directed to a time-multiplexed or time-staggered detection system for parallel channels. Instead, Yeung is directed to a **simultaneous** monitoring system for parallel channels of separations/capillaries. The parallel channels are **monitored simultaneously**, not in

a time-multiplexed or time-staggered manner as in the context of the present invention as disclosed. Yeung refers to a multiplexing approach to detection (e.g., in the Abstract), but in the context referenced in Yeung, the multiplexing detection refers to **simultaneously monitoring** the multiple capillaries (see, Abstract; and col. 1, lines 49 to 50). Yeung intention is clear, as it states at col. 9, lines 48-49: "Since all channels are monitored **at all times**, true **multiplexing** is achieved."; and at col. 14, lines 51-55: "First, truly **simultaneous multiplexing** of capillary electrophoresis can be achieved because the CCD camera **monitors all capillaries simultaneously**, resulting in data rates ...."

The simultaneous monitoring is further evident from the type of detector deployed in the Yeung system. Yeung uses a charge-coupled device (CCD) imaging system, which, by its very nature, comprises an array of detector elements. Each of the separation channels is optically matched to each pixel column on the CCD detector (see, col. 9, lines 40-43). Accordingly, a CCD detector **simultaneously monitors several channels**, not is a time staggered or multiplex manner as in the present invention.

Further, each of the separation channels is not associated with a separate light source in Yeung. Yeung teaches the illumination of several optical fiber/capillary separation channels with one light source. The one source – many fiber configuration is quite clearly stated in Yeung. For example, at col. 7, lines 31+, Yeung states that: "Depending on the power of the laser 40, the diameter of the laser beam 47, and the number and size of the optical fibers 15, the collimating means 45 can either be focusing or diverging **the laser beam 47 to irradiate the ends 42 of the optical fibers 15**. If the laser has a narrow beam of high power and the number of optical fibers is large, the microscope objective 45 can be used **to diverge and spread the laser beam 47 evenly over the ends 42 of the optical fibers 15**. If the laser 40 has a wide beam

47 of low power, it may be necessary to use the microscope objective 45, **to focus the beam 47 onto the ends 42 of the optical fibers 15**." And at col. 9, lines 26-30: "For an embodiment of 1024 capillaries, **an argon ion laser** of 1-5 Watt power or any appropriate laser of suitable power and wavelength can be used to **illuminate one end 42 of the fiber bundle**, conveniently **distributing about 0.4-2 mW of light to each fiber**."

Accordingly, because its channels are not associated with separate radiation sources, Yeung does not direct radiation to the separate channels in a predetermined sequence. Instead, Yeung refers to the selective irradiation/detection **in a particular channel**. At col. 13, lines 11-25: "Only during such time where the bands are near to the detection zone would the laser irradiation be needed. An additional electronic shutter in the beam path may be used to open synchronously with the CCD shutter, allowing light to be transmitted to the capillary only during the period of data collection, and blocking the incident beam during the time when no signal is collected." However, this channel specific selective irradiation and detection approach has nothing to do with time-multiplexed/time-staggered irradiation (e.g., controlling the plurality of radiation sources to activate in successive pulses with respect to the radiation sources) and time-multiplexed/time-staggered detection **across the many channels**, as is practiced in the present invention.

In view of the foregoing, it is abundantly clear that Yeung does not teach a detection system comprising a plurality of radiation sources, **each** associated with **one of said separation channels**, and control means for controlling the radiation sources and detecting means in a manner such that **excitation radiation is introduced at the detection zone of each separation channel in a predetermined sequence** and **radiation emission from the detection zone of**

each separation channel is detected in a time staggered/multiplexed manner, as required by claim 1 of the present application, and similarly by claims 11 and 13 of the present application.

Further, Yeung does not teach the synchronizing of pulsing of the radiation sources and detection sampling rate and period by taking into account the lag time in emitted radiation in adjacent separation channels (as required by claim 4 of the present application). Such inventive approach reduces crosstalk. Instead, Yeung reduces crosstalk by deploying spacers, i.e., capillaries coated with black ink, between separation capillaries/channels (see, col. 16, lines 21-25).

In view of the foregoing, the present invention as defined by claims 1, 11 and 13, and the claims dependent therefrom are patentable over Yeung.

c. 102(b) Rejection Based on Melman

On the onset, Applicant notes that the Examiner did not apply Melman against claims 4 and 5 of the present application. Accordingly, claims 4 and 5 are patentable over Melman, and in view of the traversal of the rejection based on Yeung, claims 4 and 5 should be allowable.

Melman also does not anticipate the claimed invention. Melman does not disclose a detection system in which the radiation sources **and** detecting means are controlled in a manner such that excitation radiation is introduced at the detection zone of each separation channel in a predetermined sequence and radiation emission from the detection zone of each separation channel is detected in a **time staggered/multiplexed manner**.

The Examiner referred to the embodiment of Figs. 1 and 11 disclosed in Melman. This embodiment is directed to a detection system in which multiple LEDs are used for the channels. However it does not include any discussion of the control of the detector with respect to the LED sources. While Melman referred to the coupling of the light from the array of LED's to the

optical fibers 16 in sequence, and the actuation of each LED in temporal sequence to improve the signal to noise ratio, it failed to provide any disclosure concerning the control of the detector with respect to the LEDs, much less an enabling disclosure of time staggered/multiplexed detection as required by the present invention. More specifically, Melman is silent on the control of the radiation sources **and** the detector in a manner such that excitation radiation is introduced at the detection zone of each separation channel in a predetermined sequence and radiation emission from the detection zone of each separation channel is detected in a **time staggered/time-multiplexed manner**.

Melman disclosed additional but distinct embodiments of detection schemes. The other distinct embodiments disclosed in Melman do not make up for the deficiencies of the embodiment of Fig. 1 and 11.

The embodiment of Fig. 13 discloses a system in which a separate detector 195 is used for each separation channel (claim 2). The control processor 197 is not configured to control the detectors **and** LEDs 192 in a time staggered/multiplexed manner (claims 1, 11 and 13). The filter 199 allows only selected light being modulated at a certain frequency of the fluorescence, to prevent crosstalk or stray emissions from neighboring channels (page 12, lines 4-10). Contrary to the Examiner's comment, this does not effect detection in predetermined detection cycles at a frequency to provide a desired detection resolution (claim 6).

The embodiment of Fig. 15 discloses a multi-wavelength detection system, in which a plurality of radiation sources 300 at different wavelengths are directed at each capillary. The plurality of radiation sources are each modulated at a different frequency by a modulator 302. A synchronous detector 316 detects a signal from the photodetector 314 only if the signal has a frequency that is defined by the modulators 302. In other words, the synchronous detector 316 operates in synchronization with the modulators 302, for **each** channel, **not across** channels. The

detectors 314 and 316 are not controlled with respect to the sources in a time staggered/multiplexed manner (claims 1, 11 and 13), and further in a predetermined sequence and pulse/frequency, simply because the different sources are not separately associated with different channels.

Accordingly, claims 1, 11 and 13, and the claims dependent therefrom, are not anticipated by Melman.

CONCLUSION

In view of all the foregoing, Applicant submits that the claims pending in this application are patentable over the references of record and are in condition for allowance. Such action at an early date is earnestly solicited. **The Examiner is invited to call the undersigned representative to discuss any outstanding issues that may not have been adequately addressed in this response.**

Respectfully submitted,

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